CHAPTER - 2

LITERATURE SURVEY

Literature survey is carried out mainly in the areas of quinoxalines and stilbenes.

2.1. Literature Survey of Quinoxalines:

Antimicrobial activity:

Kurasawa and Muramatsu et al [1] have synthesized 3-(α-chloro phenyl hydrazono) hetero aryl methyl–2-oxo-1,2-dihydro quinoxalines which have shown antimicrobial activity.

Compounds also exhibited the antifungal activity against *Pathium debaryanum*, *Pyriclaria oryzae* and *Rhizoctonia solani* at the concentrations of 100 ppm.

\[
\begin{align*}
&\text{N} \quad \text{R} \quad \text{N} - \text{NH} \quad \text{Cl} \\
&1 \text{R=} \text{COOCH}_3 \\
&2 \text{R=} \text{CONHNH}_2 \\
&\text{a. O-Cl} \\
&\text{b. m-Cl} \\
&\text{c. p-Cl}
\end{align*}
\]

The reactions of 3-(α-chloro phenyl hydrazono) hydrazine and carbonyl methyl-2-oxo-1,2-dihydro quinoxalines with triethyl orthoesters resulted in
intramolecular cyclization to give the 3-(α-chloro phenyl hydrazono-1,3,4-oxadiazol-2-yl methyl)-2-oxo-1,2-dihydro quinoxalines.

\[
\begin{align*}
N & N \\
N & O \\
\end{align*}
\]

1. \(R = H\) (O-Cl)  \\
2. \(R = H\) (p-Cl)  \\
3. \(R = CH_3\) (O-Cl)  \\
4. \(R = CH_3\) (p-Cl)

**Antifungal activity:**

Kurasawa and Muramatsu et al.[5] synthesized 1-aryl-1H- and 1-aryl-3-heteroaryl -1H-pyrazolo (3,4-b) quinoxalines (flavazoles). Flavazoles were synthesized from 3-methyl-2-oxo-1, 2-dihydro quinoxaline and the 3-triazolyl methylene-2-oxo-1, 2, 3, 4- tetrahydro quinoxaline respectively, via facile hydrazone synthesis using aryl diazonium salts. They exhibited the antifungal activity against *Pathium debaryanum*, *Pyriclaria oryzae* and *Rhizoctonia solani*.

Various 1H-pyrazolo (3, 4-b) quinoxalines have been synthesized by the direct dehydrative cyclization of the hydrazones in a diluted base or acetic acid under reflux for 2-5 hours.
Bacteriostatic activity:

Maghraby and Koraiem et al [3] synthesized pyrazolo (3, 4-d) quinoxaline dimethine cyanine dyes. The antimicrobial activity of some cyanine dyes was evaluated against the bacteria *Staphylococcus aureus*, *Staphylococcus albus*, *bacillus coagulance* and the fungi *Aspergillus niger* and *Penicillium cyclopium* employing the filter paper disc method. The structure activity relationship was demonstrated relative to the parent 3-methyl-1-phenylpyrazolo (3,4-d) quinoxaline-2-ethiodide which showed only antimicrobial activity. Introduction of a heterocyclic quaternary residue extends their biological activities of other fungi because of the extended conjugation.

Absence of quaternisation of the heterocyclic residue and pyrazolo (3, 4-d) quinoxaline moiety increases the activity. These were prepared by condensation of 3-methyl-4,5-dioxo-1-phenyl-2-pyrazoline and its 2-ethiodide with o-phenylenediamine in the presence of acetic acid afforded 3-methyl-1-phenyl pyrazolo(3,4-d) quinoxaline and it’s 2-ethiodide.

Antibacterial Activity:

Ibrahim [2] synthesized quinoxaline-2-thiones. The antibacterial activity of all the compounds synthesized were determined against gram positive and gram negative bacteria *Escherichia coli*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Pseudomonas pyocyanea*, *Serratia rhaanii*, *Staphylococcus aureus*, *Anthracoid sarcina*, *Bacillus cereus* and *Staphylococcus citreus*. It has been reported that the replacement of
carbonyl oxygen by sulphur in some heterocyclic compounds enhance their biological activity.

1. $R = H$
2. $R = \text{CH}_3$

3. $R = H$
4. $R = \text{CH}_3$

5. $R = H$
6. $R = \text{CH}_3$

7. $R = H$
8. $R = \text{CH}_3$

9. $R = \text{H}$
10. $R = \text{CH}_3$
11. $R = \text{H}$
12. $R = \text{CH}_3$

12. NH-pyrazolo
13. N-phenyl pyrazolo
14. o-isoaxazole

15. $R = \text{H}$
16. $R = \text{CH}_3$
17. $X$
18. $X$
19. $X$
20. $X$
Plant fungicidal activity:

John [35] synthesized pyrazinyl and quinoxalinyl phenylmethanones from quinoxalines and 2-lithio pyrazines. Alcohols and Pyrazinyl ketones find use as flavoring agents.

They are intermediates in the synthesis of aromatase inhibitors, plant fungicides and pyridines. Lithiobenzopyrazines used to synthesize substituted quinoxalines.

\[
\text{N} \quad \text{N} \\
\text{X} \\
\text{Li} \\
\text{C} \\
\text{N} \\
\text{OMe} \\
\text{OMe} \\
\]

Antiallergic activity:

Reddy and Krishnan et al [36] synthesized 1,6- disubstituted (1,2,4) ditriazolo (4,3-a: 3\textsuperscript{1},4\textsuperscript{1}-c) – and 2-aryl/heteroaryl (1,3,4) oxadiazino (5,6-b) quinoxalines. The reaction of 2,3 – dichloroquinoxaline (I) with various acid hydrazides (ii) in 1:2 mole ratio gives the corresponding ditriazoloquinoxalines (iv), while equimolar quantities of (i) and (ii) react together in acetonitrile / K\textsubscript{2}CO\textsubscript{3} to form the respective oxadiazinoquinoxalines (v) as exclusive product in good yields. They have reported some new ditriazoloquinoxalines possessing antiallergy activity.

\[
\text{N} \quad \text{N} \\
\text{Cl} \\
\text{RCONHNH}_2 \\
\text{NH} \\
\text{NH} \\
\text{N} \\
\text{R} = \text{a) CH}_3 \\
\text{b) CH(CH}_3)_2 \\
\text{c) CH}_3C_6H_5 \\
\text{d) C}_6H_5 \\
\text{V)} R = \text{a) C}_2H_5 \\
\text{b) 2,4- di ClC}_6H_3
\]
CNS depressant activity:

Bansal and Srinivas et al [6] synthesized several new 2-arylamino-4-oxo (1,3) thiazino (5,6-b) quinoxalines. Several new 2-arylamino-4-oxo (1,3) thiazino (5,6-b) quinoxalines have been synthesized by reacting ethyl 2-chloroquinoxaline-3-carboxylate with various aryl thioureas. The compounds possess CNS depressant activity. New thiazino (5,6-b) quinoxaline are prepared by the reaction of ethyl 2-chloroquinoxaline-3-carboxylate with various aryl thioureas. They exhibited 23 to 60% sedative, 40 to 100% ataxia effects and 36 to 91% reduction in locomotor activity in mice.

![Chemical structure](image)

Antimalarial activity:

Venugopalan and Souza et al [8] synthesized Pyrido (3,2-f) quinoxalines and their N-oxides. Unsubstituted, 2,3-dimethyl, and 2,3-diphenyl 10-chloro pyrido (3,2-f) quinoxalines have been prepared and converted to 10-substituted amino and Mannich base derivatives. Pyrido (3,2-f) quinoxalines having the diethylamino-propylamino group at 10-position, showed moderate activity at 50mg/kg.

![Chemical structure](image)
Among the Mannich bases, the following compounds showed 100% activity.

a)  

b)  

c)  

The following compounds showed moderate activity.

Antiviral agent:
Campiani and Aiello et al [9] synthesized quinoxaliny1 ethyl pyridyl thioureas as potent non-nucleoside HIV-1 reverse transcriptase inhibitors.
Antileprotic activity:

Krishnan and Chowdary [37] synthesized 2-phenylsulphonyl-3-styrylquinoxalines. 4,4'-diaminodiphenylsulphone (DDS), the sulphonyl moiety has received much attention as a potential pharmacophore in medicinal chemistry. Sulphones exhibit antibacterial, antitubercular and antimalarial properties.

\[ \text{O-phenylenediamine} \text{ with pyruvic acid or sodium pyruvate to yield 3-methylbenzo-1H-dihydropyrazine-2-one. Later on condensation with aromatic aldehydes give 3-styrylquinoxaline-1H-2-one. The reaction of those with POCl}_3 \text{ in the presence of catalytic amount of DMF yields 2-chloro-3-styryl quinoxaline, which on reaction with thiophenol in the presence of triethylamine in methanol gives 2-phenylthio-3-styryl quinoxaline. Oxidation of this with H}_2\text{O}_2 \text{ in the presence of acetic anhydride affords 2-phenylsulphonyl-3-styrylquinoxaline.} \]

\[
\text{R A X Y Z} \\
a. 7-F \text{ CH N C CH} \\
b. 9-F \text{ CH N C CH} \\
c. 7-Cl \text{ CH N C CH} \\
d. H \text{ N N C CH}
\]

\[ \text{Antiinflammatory Activity:} \]

Chen and Arthr et al [4] synthesized anilino 5-azaimidazoquinoxaline analogues possessing in vivo anti-inflammatory activity. T cell mediated immune responses play an important role in the pathogenesis of many immunological
disorders, including but not limited to rheumatoid arthritis, asthma, multiple sclerosis, inflammatory bowel disease, systemic lupus erythematosus, psoriasis, and transplant rejection. Immune responses in T cells are initiated by the interaction of the T cell receptor (TCR) with an antigen bound to glycoprotein encoded by the major histocompatibility complex (MHC).

Antitumor agents:

Stuart and Lisa et al [7] synthesized 2-{4-[2quinoxalinyl] Oxy} phenoxy} propionicacid. Compound1 is the highest and broadly active antitumor agents have been evaluated in their laboratories. The mechanism of action is not known it was found that changes in the nature and location of substituents in ring A of 1 induced significant differences both in vitro and the in vivo activities of the 2-{4-[2quinoxalinyl]oxy} phenoxy}propionicacid. Thus seven halogen derivatives proved to be the most active compounds exhibiting an order of relative antitumor activity of F~ Cl~ Br> I, whereas the 3,5 and 6 and 8 regioisomers of 1 were essentially all inactive.
Antiamoebic agents:

Nagarajan and Parthasarathy et al. [11] synthesized s-Triazolo[3,4-a]quinoxaline from 2,3-dichloro-6-nitroquinoxaline. Displacement reaction of 2,3-dichloro-6-nitroquinoxaline with 1-methylpiperazine in the hot condition to give bis-derivative.
Antimycobacterial agents:

Lainne and Seitz et al [37] synthesis and anti-mycobacterial activity of pyrazine and quinoxaline derivatives. Lainne and Seitz et al synthesized pyrazine and quinoxaline derivatives. Different derivatives of quinoxaline have been synthesized and activity against *Mycobacterium avium* (MAC) and *M. tuberculosis* (Mt) are reported. PZA is prescribed as one of the front-line agents for the treatment of Mt. They include the use of four drugs, rifampicin, isoniazid, PZA and either streptomycin or ethambutol. PZA acts by inhibition of the fatty acid synthetase 1 (FASI) of Mt. PZA is considered to be a prodrug of POA and is believed to be Mt active inhibitor.

Aldosereductase inhibitory activity:

Reinhard and John [36] have synthesized N-1, N-4-Disubstituted 3,4-dihydro-2 (1H) -quinoxaline derivatives. They discovered 4-acetyl -3,4-dihydro-2 (1H) -quinoxaline-1-acetic acid 1 inhibited bovine lens aldose reductase (1) and prevented sorbitol accumulation in the sciatic nerves of diabetic rats at very high doses. This finding indicated that compounds of this type might be useful in the therapy of complications of diabetes mellitus and they synthesized additional
compounds in the heterocyclic class. They replaced the acetyl group with more lipophilic groups such as benzoyl, benzene and sulphonyl with alkyl groups.

The target compounds and some of the synthetic intermediates were tested for their ability to inhibit bovine lens aldose reductase in vitro. These compounds were also assayed for their ability to suppress the sorbitol formation in sciatic nerves of streptozotocin-diabetic rats in vivo.

\[
\begin{array}{ccc}
\text{(CH}_2\text{n.COOR}_1
\
\end{array}
\]

<table>
<thead>
<tr>
<th>Compound no.</th>
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<td>Ac</td>
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<td>1</td>
</tr>
<tr>
<td>2</td>
<td>PhCO</td>
<td>H</td>
<td>-</td>
</tr>
<tr>
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<td>PhCO</td>
<td>Et</td>
<td>1</td>
</tr>
<tr>
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<td>Et</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Ac</td>
<td>H</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>Ac</td>
<td>Et</td>
<td>2</td>
</tr>
</tbody>
</table>

**A$_3$ Adenosine receptor antagonists:**

Vittoria and Daniela et al [39] synthesized human A$_3$ Adenosine receptor antagonists. They synthesized triazoloquinoxaline-1,4-diones and triazolo (4,3-a) quinoxalin-4-amino-1-ones. Some compounds were potent, selective A$_3$ receptor antagonists. A new series of triazoloquinoxaline derivatives were described. The neuromodulator adenosine exerts many biological functions by activation of G-protein-coupled receptor subtypes, currently classified into A$_1$, A$_{2A}$, A$_{2B}$, and A$_3$ subtypes. All four adenosine receptor subtypes have been characterized on a pharmacological level and cloned.
Antitumor agent:

Stuart and Lisa et al [7] synthesized 2-{4-[2quinolaxinyl] oxy phenoxy} propionicacid. They found this as active antitumor agents.

```
Y=Cl  V=X=H,  R=H    X=Cl  V=Y=H,  R=C_2H_5
Y=Cl  V=X=H,  R=CH_3 X=Cl  Y=Z=H,  R=CH_3
```

All newly synthesized analogues were evaluated in vitro, disk diffusion soft agar colony formation assay to determine the cytotoxicity against leukemias, solid tumors and normal cells. Many of the analogues of 1 that were tested in mice exhibited only modest cytotoxicity and tumor selectivity in tissue culture.

Analgesic activity:

Parke [42] synhesized Perhydro-2(1H)-quinoxalinones and per hydro pyrrolo[1,2-a]quinoxaline-4(5H)-one derivatives. Research into the development of drugs for the alleviation of pain has focused recently on the identification of chemical structures that bind to kappa opioid receptors in the brain. As part of the research program aimed at producing novel kappa opioid structures. The most selective kappa opioid compound is the 1,2-amino amide. The target compounds were 5 and 10 where the 2 nitrogen atoms are incorporated into a piperazine ring to increase rigidity. Aziridines have been reported previously to undergo ring cleavage reactions with a variety of nucleophilic reagents (5) including primary or secondary amines (6,7) , hydrogen halides (6), alcohols (5,6) and inorganic azides (8). Treatment of aziridines with nucleophiles possessing a latent electrophilic site is also known this being a method of constructing heterocyclic compounds (9).
Synthesis of Pyridazino[3,4-b]quinoxaline:

Ho and Yoshihisa et al [42] synthesized Pyridazino[3,4-b]quinoxaline The reaction of 2,6-dichloroquinoxaline 4-oxide with methylhydrazine gave 6-chloro-2-[1-methyl hydrazino] quinoxaline 4-oxide. When they react with dimethyl acetylenedicarboxylate or 2-chloro acrylonitrile resulted in the 1,3-dipolar cycloaddition reaction to afford 7-chloro-3,4-bis methoxycarbonyl-1-methyl-1,2dihydropyridazino[3,4-b]quinoxaline or 6-chloro-3-hydroxy methylene-1-methyl-2,3-dihydro-1H-pyrazolo[3,4-b]-quinoxaline hydrochloride respectively.
Synthesis of 2-Substituted 1H-Imidazo[4,5-f]quinoxalines:


Synthesis and tautomeric behavior of 3-(pyrazolylhydrazinomethyl)-2-oxo-1,2-dihydroquinoxalines:

Ho and Yoshihisa *et al* [42] synthesized 3-(pyrazolyl hydrazinomethyl)-2-oxo-1,2-dihydro quinoxalines. The synthesis and tautomeric behavior of 3-9 (pyrazolylhydrazonemethyl) -2-oxo-1,2-dihydroquinoxalines is described.
The reaction of the quinoxaline 4 with the pyrazole-5-diazonium salt 5 afforded the hydrazine 2. The reaction of the quinoxaline 6 with the pyrazole-5-diazonium salt 7 furnished the hydrazine 3, whose refluxing in triethylamine and N,N-dimethylformamide resulted in cyclization to give 8-cyano-7-methyl-4-oxo-3-(3-oxo-3,4-dihydroquinoxaline-2-yl)-4,6-dihydropyrazolo[5,1-c][1,2,4,5]triazine 8.

**Synthesis of 3'-Formyl-2-oxo-1,2-dihydroquinoxaline:**

Yoshihisa and Kaoru et al [43] synthesized 3'-Formyl-2-oxo-1,2-dihydroquinoxaline Chlorophenylhydrazones. The tautomerism of 3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline has been studied by means of ^1^H-NMR and UV spectroscopy tautomers A and B co-exist in DMSO solution.

**Glycine Site receptor antagonists:**

Jonathan and David et al [44] synthesized 1,4-Dihydro-(1H,4H)-quinoxaline-2,3-diones. L-glutamic acid is an important excitatory amino acid in the central nervous system. Possible therapies for thrombo-embolic stroke, injury, Parkinson’s and Alzheimer’s diseases etc.
Parallel Synthesis of 3,4,7-trisubstitued 3,4-Dihydroquinoxaline-2-ones:

Edgardo and Brian et al [45] synthesized 3,4,7-Trisubstitued 3,4-Dihydroquinoxaline-2-ones. Parallel synthesis of new methodology of 3,4,7-trisubstitued 3,4-dihydroquinoxaline-2-ones were described.

Synthesis of quinoxaline-2-ones linked to pyrazolines and pyrazoles:

Ferfira and Ahabchane, et al [46] synthesized quinoxaline-2-ones linked to pyrazolines and pyrazoles. They synthesized new derivatives of quinoxaline which are found to show pharmacological activities.
NMDA Receptor Antagonists:

Shu-Kun [47] in 1996 synthesized Quinoxaline-2, 3-diones NMDA Receptor antagonists. At 50-80°C, 1,2-diamino aromatic compounds yields quinoxalines-2,3-diones in diethyl oxalate by rotary evaporation as precipitates.

Several publications recently described that certain quinoxaline-2-ones [3] and quinoxaline-2,3-diones [1,2] were highly potent NMDA receptor antagonists and are highly potent. Quinoxaline-2-ones quinoxaline-2,3-diones are mainly synthesized by condensation of aryl diamines (o-phenylenediamines) with various ketoacid derivatives [4], they can also prepare by photo rearrangement of quinoxaline-1,4-dioxides [5].
Synthesis of Pyridazino[3,4-b]quinoxalines:

Ho and Minako et al [50] synthesized Pyridazino[3,4-b]quinoxalines. The Pyridazino [3,4-b] quinoxalines and pyrazolo [3,4-b] quinoxalines were synthesized by 1,3-dipolar cyclo addition reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide with dimethyl or diethyl acetylenedicarboxylate and 2-chloroacrylonitrile, respectively.

![Chemical structures](image1)

Synthesis of condensed quinoxalines:

Sabnis and Rangnekar [49] synthesized condensed quinoxalines. Quinoxalines are commercially important as antibiotics, antagonists, agrochemicals, fungicides, herbicides etc. They reported the synthesis of novel heterocyclic dyes and fluorescent brighteners such as thiophenes, benzothiophenes, thiazoles and their applications on synthetic fibers.

![Chemical structures](image2)
Synthesis of Pyrido[1',2':1,2]imidazo[4,5-b]quinoxalines:

Kiyoshi and Hideki et al [52] synthesized Pyrido[1',2':1,2]imidazo[4,5-b]quinoxalines by the cyclizations of 2-aminopyridines and 2,3-dichloroquinoxalines with various pyridine substitutes. Most of the products revealed the interesting fluorescent properties.

\[
\text{X = H, Cl, COC}_6\text{H}_5, \text{NO}_2
\]

Synthesis of N, N-1, 1',4,4'- (bis-ethylene) 1, 2, 3, 4 - bistetrahydroquinoxaline:

Khan and Rastogi et al [51] synthesized N, N-1, 1',4,4'- (bis-ethylene) 1,2,3,4-bis-tetrahydro quinoxaline starting from 1,2,3',4-tetrahydroquinazoline. 1,2,3', 4-tetrahydroquinazoline (1) needed for the synthesis was prepared in 80% yield. The amine1 was treated with ethylene dibromide in the presence of dimethyl formamide
and potassium carbonate at elevated temperature to get the desired product 6 in one step.

**Synthesis of 1-phenyl-4-oxo[1,2,4]triazolo[4,3-a]quinoxaline from 2-chloro-3-(2'-benzylidenehydrazino)-quinoxaline:**

Krishnan and Chowdary [52] have synthesized 1-phenyl-4-oxo[1,2,4]triazolo[4,3-a]quinoxaline from 2-chloro-3-(2'-benzylidenehydrazino)-quinoxaline by dehydrogenative cyclization using cupric acetate. Quinoxaline derivatives and fused quinoxalines are reported to possess interesting pharmacological properties. They have reported the synthesis of a number of 1-aryl-4-alkoxy/phenoxy-[1,2,4]-triazolo [4,3-a]quinoxalines.
Multiple-drug-resistance antagonists:

David and Charles [55] have made SAR studies of substituted quinoxalines as multiple-drug-resistance antagonists. The development of tumor resistance to many chemotherapeutic agents is a problem in the clinical treatment of cancer. This was found that Quinoxaline showed partial resistance to chemotherapeutic agents.
Daniela and Vittoria, et al [54] synthesized 7-chloro-4,5-dihydro-8-(1,2,4-triazol-4-yl)-4-oxo-1,2,4-triazolo[1,5-a]quinoxaline-2-carboxylates. They were having selective AMPA receptor antagonistic activity. Glutamate is probably the major excitatory transmitter in the CNS, but it is also likely to be involved in many pathological processes. The stimulation of the ionotropic glutamine receptors, i.e., N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors (KA).
**Antibacterial and anti-HIV agents:**

Patel and Chikhalia [55] have synthesized non-heterocyclic and heterocyclic entities as anti-HIV and antibacterial agents. 2-[(2-(3,4-dimethoxy phenyl ethyl amino)-2-oxo ethyl]amino]-4,6-diaryl pyrimidines and 3-4-dimethoxy-1-[(2-aryl/alkyl amino)-2-oxoethyl]amino]-ethyl benzene has been prepared and tested for their anti-HIV and antibacterial activities. Different non-heterocyclic entities 3,4-dimethoxy – 1 - [(2-aryl/alkyl amino)-2-oxoethyl]amino] - ethylbenzenes were synthesized by condensing 3,4-dimethoxy phenyl ethyl amine and N-chloroacetanilide derivatives of various amines and different heterocyclic entities.

![3,4-Dimethoxy phenyl ethyl amine](image)

**Synthesis of novel 1-aryl-1H-pyrazolo[3,4-b]quinoxlines:**

Yoshihisa and Kaoru, et al [56] synthesized 1-aryl-1H-pyrazolo[3,4-b]quinoxlines. The reactions of 3-methyl-2-oxo-1,2-dihydroquinoxaline with chlorophenyl diazonium salts afforded the hydrazones whose chlorination with phosphorus chlorides gave the dichlorides. Refluxing of the dichlorides and base in N,N-dimethylformamide provided the 1-aryl-1H-pyrazolo[3,4-b]quinoxlines.

![1-ary-1H-pyrazolo[3,4-b]quinoxlines](image)

**Synthesis of substituted γ-lactones:**

Hans and Manning et al [57] synthesized substituted γ-lactones by reduction of 4-aroyl-3-hydroxy-2-(5H)-furanones. The reduction of 4-aroyl-3-hydroxy-2-(5H)-furanones was found using various reducing agents. 4-aroyl-3-hydroxy-2-(5H)-
furanones reacts with sodium borohydride with the loss of water to get 4-(arylmethylene)-2,3-(4H,5H)-furandiones. Charcoal or platinum supported on palladium chloride transforms 4-aryloxy-3-hydroxy-2(5H)-furanones to 4-benzyl-3-hydroxy-2(5H)-furanone.

\[\text{Preparation of 6-Substituted Quinoxaline JSP-1 inhibitors by microwave accelerated Nucleophilic substitution:}\]

Li and Beiying et al. [58] synthesized 6-Substituted Quinoxaline JSP-1 inhibitors by using the computer-controlled microwave technique. These are found to show different biological activities such as angiotensin II receptor antagonists, antiinfection agents, AMPA/Glycine receptor antagonists, and immunomodulating agents.

<table>
<thead>
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<th>R2</th>
<th>R3</th>
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<td>H</td>
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</tr>
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</tr>
<tr>
<td>7</td>
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<td>Piperidine</td>
</tr>
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</table>
Synthesis and tautomeric behaviour of 3-(pyrazolylhydrazonomethyl)-2-oxo-1, 2-dihydroquinoxalines:-

Yoshihisa, and Ho, et al [59] synthesized 3-(pyrazolyl hydrazo no methyl)-2-oxo-1,2dihydro quinoxalines. The synthesis and tautomeric behaviour of 3-9(pyrazolylhydrazonomethyl)-2-oxo-1, 2-dihydroquinoxalines is described.

The reaction of the quinoxaline 4 with the pyrazole-5-diazonium salt 5 afforded the hydrazone 2. The reaction of the quinoxaline 6 with the pyrazole-5-diazonium salt 7 furnished the hydrazone3, whose refluxing in triethylamine and N,N-
dimethylformamide resulted in cyclization to give 8-cyano-7-methyl-4-oxo-3-(3-oxo-3,4-dihydroquinoxaline-2-yl)-4,6-dihydropyrazolo[5,1-c][1,2,4]-triazine.

2.2. Literature Survey of Stilbenes:

Ahn and Kim et al [42] carried out the extensive literature survey made on the subject, revealed that there Like have been a number of reports concerning isolation of stilbene from various plant sources polygonum roots, peanuts seeds, berries, grapes, vaticarasaka etc.

Also, many scientists have carried out the synthesis and biological activities of stilbene derivatives, which revealed that stilbene plays a significant role in the biomedical field. Pharmacological Studies have established that stilbene inhibits the synthesis of eicosanoids by platelets, reducing incidence of coronary heart disease. It also has shown significant Cedric and Charles et al [63] anticancer, Brown and Copp et al [23] anti fungal, Marek and Norbert et al [26] antibacterial, Cedric and Charles et al [63] anti oxidant, Arun Sethi [28] anti-inflammatory, Ashutosh Kar [29] anticonvulsant activity.

Anti fungal activity:

Cardona and Fernandez et al [23] have been reported that synthesized stilbene derivatives have shown anti fungal activity. In this paper they described the synthesis of the cis and trans-isomers of the stilbenes (1a-1d) because of the considerable biological interest of these compounds and final proof of the structure of 3, 3\textsuperscript{1}, 5, 5\textsuperscript{1}-tetra hydroxy-4\textsuperscript{1}-methoxy stilbenes.

\begin{align*}
\text{trans-1a-1d} & \quad \text{cis-1a-1d} \\
\text{where} & \quad \text{where} \\
R_1 = & \quad R_1 = H \\
R_2 = & \quad R_2 = OCH_3 \\
R_3 = & \quad R_3 = OR; \quad R = Si(CH_3)_2 t\text{-but} \\
\end{align*}
Anticancer activity:

Pace-Aseiak and Hash et al [25] have reported that synthesized stilbene derivatives have shown anticancer activity. In this paper they described a series of stilbenes has been prepared and tested for cytotoxicity in the five human cancer cell lines A-549 non-small cell lung, MCF-7 breast, HT-29 colon, SKMEL-5 melanoma and MLM melanoma.

![cis-stilbenes](image)

where; $R_1 = 3,4,5 \text{ (OMe)}_3$

$R_2 = 4\text{-OMe}$

![trans-stilbenes](image)

$R_1 = 3,4,5 \text{ (OMe)}_3$

$R_2 = 4\text{-OMe}$

Antiplatelet aggregation:

Orsini and Francesca et al [60] carried out synthesis, and activity of antiplatelet aggregation 3-O-$\beta$-D-glucopyranoside of resveratrol and its related compounds.

![Quercitin](image)

Inhibitory activities of stilbene:

Ahn and Kim et al [62] carried out an inhibitory activity of stilbene by expression of cell adhesion molecules on THP1 cells from medicinal plants.
Antitumor evaluation of hydroxylated (e)-stilbenes:

Cedric and Charles et al [63] carried out a new synthesis, anti tumor evaluation and apoptosis-Inducing activity of hydroxylated (E)-stilbenes. They developed a strategy by adopting Horner- Wadsworth-Emmons olefination chemistry to produce new products in parallel solution phase synthesis so as to avoid its disadvantage.

![E- resveratrol](image1)

![Z - Combretastatin](image2)

Anticancer activity:

Mark and Nagarathnam et al [64] have reported that synthesized and evaluation of stilbene and dihydrostilbene derivatives inhibit tubulin polymerization.

![Z - Combretastatin](image3)

![piceatannol](image4)

![E- Combretastatin](image5)

![Dihydro Combretastatin](image6)
Antimicrobial and antitubulin activities:

George and Mathew et al [65] carried out an anti neoplastic agent such as 465 sodium resverastatin phosphate which results from the Resveratrol structural modification. Antimicrobial and antitubulin activities were evaluated for selected compounds.

\[
\begin{align*}
\text{MeO} & \quad \text{Y} & \quad \text{MeO} \\
\text{MeO} & \quad \text{OMe} & \quad \text{MeO}
\end{align*}
\]

\[
\begin{align*}
\text{R} & = \text{H} & \text{Y} & = \text{CIS - CH=CH} \\
\text{R} & = \text{H} & \text{Y} & = \text{CO}
\end{align*}
\]

Synthesis of trans-stilbenes

Novelli and Bonafede et al [66] carried out a new synthesis of Trans-stilbenes. In this paper they described an increase in the number of methoxy groups promotes the elimination reaction, giving generally better yields of stilbenes and reducing the reaction time.

\[
\begin{align*}
\text{CH}_2 & \quad \text{R}_1 & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{NH} & \quad \text{CO-R}_4
\end{align*}
\]

\[
\begin{align*}
\text{R} & = \text{H} & \text{R}_1 & = \text{H}, 2,3,4-\text{Cl,F}, 2-\text{CH}_3 \\
\text{R}_2 & = \text{H}, 3-\text{OCH}_3 & \text{R}_3 = \text{N(CH}_3)_2, \text{N(CF}_3)_2 & \text{n} = 2,3,4,5
\end{align*}
\]

Anticonvulsant activity:

Ryoji and Akhiro et al [27] have reported that substituted (W-Amino alkoxy) derivatives of stilbene shows anticonvulsant activity as a new class of drugs.

\[
\begin{align*}
\text{R}_1 & = \text{H}, 2,3,4-\text{Cl,F}, 2-\text{CH}_3 \\
\text{R}_2 & = \text{H}, 3-\text{OCH}_3 \\
\text{R}_3 & = \text{N(CH}_3)_2, \text{N(CF}_3)_2
\end{align*}
\]
Synthesis of Stevens by reduction:

Donald and Ballard et al [67] have reported that preparation of products by benzoin reduction.

\[ \text{CH}_2\text{OH} \]

\[ \text{CO} \]

\[ R_1 = H \]

\[ R_2 = \text{OCH}_3 \]

Cytotoxic activity:

Mark and Nagarathnam et al [34] carried out the synthesis and evaluation of antimitotic and cytotoxic agents, e.g. analogues of (Z)-1-(4-methoxy phenyl)-2-(3,4,5-trimethoxy phenyl) ethane.

Diaryl ethylene synthesis:

Wood and Bacon et al [69] carried out the Diaryl ethylene synthesis which are symmetrical.

Antimicrobial activity

Brown and Copp et al [24] have been reported that the stilbene derivatives have anti-microbial activity.

Mark and Nagarathnam et al [34] carried out a synthesis of flavonoid analogies which shows inhibitory activity of protein-tyrosine kinase.
Chemopreventive properties:
Holmes and Baldwin, et al [70] carried out a synthesis of trans resveratrol are associated with inhibition of kappa b kinase activation.

Synthesis of terphenyls:
Daniela and Vittoria et al [54] have been reported the synthesis of biologically active stilbenes of substituted terphenyls through a double Suzuki cross-coupling.

Wittig reaction:
Hiroshi and Katsushi et al [71] carried out wittig reactions which explains sterioselectivity and reactivity of benzylidenetriphenyl phosphorane with substituted benzaldehydes.

Stilbene modulators:
Phillippe and Robert et al [72] carried out a synthesis and biological activities of resveratrol as derivatives of new stilbene modulators of aryl hydrocarbon.
**Antithrombotic activity:**

Ryoji and Akhiro *et al* [27] have been reported that [2-(W-amino alkoxy) phenyl] ethyl] benzenes exhibits antithrombotic and platelet aggregation.

![Chemical structure](image)

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>R2</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>2-OCH3</td>
<td>H</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>2-OCH3</td>
<td>H</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>3-Cl</td>
<td>H</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>3, 4Cl</td>
<td>H</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

**Anti-inflammatory activity:**

James and Dallas *et al* [73] carried out the synthesis of new Anti-inflammatory agents which are Potent. E.g. propionic acids and dibenztroponeacetic acid.

![Chemical structure](image)

R = CH₃COOH, CH₂COOCH₃, CH(CH₃)COOH, CH(C₂H₅)COOH

Justin and Waylon *et al* [74] have been reported that trans-stilbene substituted products which also includes resveratrol analogues.

![Chemical structure](image)

R = CH₃, H

**Anticancer activity:**

Filippo and Giusy *et al* [75] carried out a synthesis of a Resveratrol derivatives with high ceramide-medicated proapoptotic activity of human breast cancer cells.
Structure of Stilbene and Naphthalene-type resveratrol analogues

RES
1) (R=H, R'=H)
2) (R=Me, R'=H)
3) (R=Me, R'=Me)
4) (R=H, R'=H)
5) (R=Me, R'=H)
6) (R=Me, R'=Me)

Synthesis of hydroxy stilbenoids:
Shadakhari and Rele et al [76] carried out a low valent titanium mediated synthesis of hydroxy stilbenoids for some new observations.

Synthesis of polyphenolic glycosides:
Orsini and Francesca et al [60] carried out a synthesis of biologically active polyphenolic glycosides (combretastatin and resveratrol series). In this paper, they described the corresponding glycosides, and related compounds have been synthesized via Wittig reaction followed by glycosylation under phase transfer catalysis. Most of the compounds synthesized have been tested with respect to biological activity (cytostatic, cytotoxic, Antimitotic, Neurotoxic, Antiplatelet aggregation activity).
Synthesis of resveratrol octamer:

Ito and Tanaka et al [77] carried out a new resveratrol octomer, vateriaphenol A in vateriaindica.

Human cytochrome P 450 1B1 Inhibitors:

Sanghee and Hyojin et al [78] carried out a design synthesis, and discovery of novel trans stilbene analogues as potent and selective human cytochrome P 450 1B1 Inhibitors. They described in this paper the CYP1 Inhibition of synthesized trans stilbene analogues and our discovery of 2, 3^1, 4, 5^1- tetra methoxy stilbene to be a selective and potent CYP 1B1 inhibitor.

Apoptosis-Inducing agents:

Marinella and Daniela et al [79] have reported that synthesized and reported biological evaluation of resveratrol and analogues as Apoptosis-Inducing agents.
Synthesis of neoflavonoid analogues of combretastatin:

Baily and Christine et al [80] carried out a synthesis and biological evaluation of 4-Aryl coumarin analogues of combretastatins. In this paper they described synthesis of neoflavonoid analogues of combretatin A-4.

Dela Lastra and Villegas et al [81] carried out an Anti aging and Anti-inflammatory activities of resveratrol.

Inhibition of cell proliferation:

Poussier and Cordova et al [82] have been reported that resveratrol inhibits cell proliferation of vascular smooth muscle and induction of apoptosis. Inhibition of resveratrol is dose dependent. This also explains about wine drinking beneficial effect.
Anticancer activity:

Zhou and Chen et al [83] have been reported that the anticancer activity of Resveratrol on implanted human primary gastric carcinoma cells in nude mice. In this article they investigated the apoptosis of implanted primary gastric cancer cells in nude mice induced by resveratrol and the relation between this apoptosis and expression of bcl-2 and bax.

Potter and Patterson et al [84] have been reported that conversion of resveratrol to piceatannol via cytochrome P450 enzyme.

Anti-inflammatory activity:

Chen and Shan et al [85] carried out a synthesized and anti-inflammatory activity of resveratrol analogs. In this paper they described the synthesis of seventeen novel resveratrol derivatives. Their anti-inflammatory activities were tested on xylene induced mouse ear edema.

1) \( R = \text{Me}, \ R' = \text{H} \)
2) \( R = \text{H}, \ R' = \text{Me} \)
3) \( R = \text{Me}, \ R' = \text{Me} \)
Antioxidant activity:

Fremont and Belguendouz et al [86] have been reported that the antioxidant activity of resveratrol and alcohol-free wine polyphenols related to LDL oxidation and polyunsaturated fatty acids.

\[
\begin{align*}
\text{3,4,5 Trihydroxy stilbene}
\end{align*}
\]

Murias and Jager, et al [87] carried out an antioxidant, preoxidant and cytotoxic activity of hydroxylated resveratrol analogues.

Antifungal activity:

Seppanen and Syrijala et al [88] have been reported that the antifungal activity of stilbene in vitro bioassays and in transgenic populus expressing a gene encoding pinosylvin synthase.

\[
\begin{align*}
\text{R1} & \quad \text{R2} \\
4'\text{-OMe} & \quad \text{OMe} \\
4'\text{-Cl} & \quad \text{Cl} \\
4'\text{-F} & \quad \text{F} \\
3'\text{-OMe} & \quad \text{Cl}
\end{align*}
\]

Antimicrobial activity:

Wyrzykiewicz and Blaszczyk et al [89] carried out a synthesis and antimicrobial activity of (E)-acetoxy Stevens and alpha, alpha1-dibromoacetoxy bibenzyls and their antimicrobial activity are reported.
**Vasorelaxant activity:**

Santigo and Quezada *et al* [91] have been reported that design, synthesis, platelet antiaggregatory and vasorelaxant activities of hybrids of coumarin-resveratrol. In this article they explained about synthesized dimethoxy derivatives of coumarin-resveratrol and hybrid 4 of coumarin-resveratrol.

![Chemical structure](image)

**Antioxidant activity:**

Olas and Wachowicz *et al* [92] carried out a resveratrol a phenolic antioxidant with effects on blood platelet functions. The main purpose of this article is to provide an overview of the currently available evidence of antiplatelet properties of resveratrol.

Lu and Ho *et al* [93] have been reported that resveratrol analogue 3, 4, 5, 4\(^1\)-tetra hydroxy stilbene induces gene expression of pro-apoptotic P\(^{53}\)/bax. This paper explains that the above derivatives do not affect normal cells, but inhibits the transformed cell growth.

**Anticancer nutrient:**

Signorelli and Ghidoni *et al* [90] carried out a resveratrol as an anticancer nutrient molecular basis, open questions and promises. In this paper they discussed Resveratrol potential as anticancer chemo preventive and chemotherapeutic agent and its implication on the pro survival versus pro death. Aza-Stilbene derivative such as resveratrol acts in slowing and prevention of diseases such as cancer, heart diseases and inflammation.
Effect of stilbene derivative on superoxide generation and enzyme release from human neutrophils in vitro:

Macickova and Pecivova et al [31] revealed that superoxide generation decreased based on the dose of the Pterostilbene. The pterostilbene effect was more on superoxide generation in comparison to release of the MPO. The effect of pterostilbene may be beneficial in reducing inflammation.

Nanoemulsion of stilbene:

Zhang and Gao et al [94] have synthesized 3,5-dihydroxy-4-isopropylstilbene nanoemulsion in the laboratory and isopropyl myristate (IPM) was bought from Shanghai Leasun chemical co. Ltd (Shanghai, China). Various surfactants such as polyoxyethylene sorbitan fatty acid esters (Tween-80) and polyoxyethylated castor oil (EL-40) were purchased from Tianjin Yongda chemical reagent development center (Tianjin, China). Methanol was chromatographically pure and purchased from Kangkede (Tianjin, China). Other chemical reagents were all analytically pure grades and purchased from the Shijiazhuang Modern Reagent Co (Shijiazhuang, China).
Soya bean salad oil, olive oil and peanut oil were all of food grade and purchased from COFCO (Tianjin, China). Water was twice distilled.

Resveratrol anti-cancer effect:

Hagiwara and Kosaka *et al* [95] have been reported that stilbene derivatives promote Ago2-dependent tumor-suppressive micro RNA activity. CSC fraction is reduced by resveratrol. MRNAs mediate resveratrol anti-cancer effects.

Chowdhury and Kishino *et al* [68] a total of eleven stilbenes [1-6] and flavonoids [7-11] were investigated for their tumor-specific cytotoxicity and apoptosis-inducing activity, using four human tumor cell lines (squamous cell carcinoma HSC-2, HSC-3, submandibular gland carcinoma HSG and promyelocytic leukemia HL-60) and three normal human oral cells (gingival fibroblast HGF, pulp cell HPC, periodontal ligament fibroblast HPLF). All of the compounds, especially sophorastilbene A [1], (+)-alpha-viniferin [2], piceatannol [5], quercetin [9] and isoliquiritigenin [10], showed higher cytotoxicity against the tumor cell lines than normal cells, yielding tumor-specific indices of 3.6, 4.7, >3.5, >3.3 and 4.0, respectively. An undetectable expression of Bcl-2 protein in control and drug-treated HSC-2 cells may explain the relatively higher sensitivity of this cell line to stilbenes and flavonoids.